U.S. FOOD & DRUG ADMINISTRATION

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NOV 07 2019

Re: Docket No. FDA-2019-P-1679

Dear Mr. Lassman,

This letter responds to the citizen petition (Petition)[1] dated April 5, 2019, that you submitted to the Food and Drug Administration (FDA or the Agency) on behalf of Braeburn, Inc. under the docket number referenced above (Docket). In the Petition, you request that FDA:

1. Revoke Indivior Inc.'s[2] orphan-drug designation for Sublocade[3] (buprenorphine) for treatment of opiate addiction in opiate users (currently referred to as opioid use disorder (OUD))[4]; and
2. Refuse to grant orphan-drug exclusivity to Sublocade, or withdraw such exclusivity, if already granted.

We have also carefully reviewed your submissions to the docket dated May 23, 2019, August 15, 2019, August 22, 2019, and October 11, 2019, as well as the numerous other comments submitted to the docket and additional relevant information available to the Agency. For the reasons set forth below, we grant the petition in part, and will revoke, as improperly granted, Indivior's orphan-drug designation for buprenorphine for treatment of "opiate addiction in opiate users" pursuant to 21 CFR § 316.29(a)(3).[5] Accordingly, we did not need to consider, and have

[1] *Available at* https://www.regulations.gov/docket?D=FDA-2019-P-1679.

[2] Indivior's predecessor Reckitt & Colman Pharmaceuticals, Inc. submitted this orphan-drug designation request for buprenorphine and held the orphan-drug designation in that name until 2015. Throughout this response, we will refer to the sponsor as Indivior, including during the time period covered by this Petition.

[3] Sublocade is the proprietary name for buprenorphine extended-release injection for subcutaneous use marketed by Indivior under NDA 209819.

[4] "Opiate addiction" is no longer a commonly used term in clinical practice. "Opiate addiction" is currently termed opioid dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) DSM-IV diagnostic criteria, or moderate to severe opioid use disorder (OUD) as defined by DSM-V diagnostic criteria. Because "opiate addiction" was the term used at the time the request for designation was submitted, throughout this response we will use this terminology when referring to the disease for which FDA granted designation to buprenorphine. When discussing the disease generally, we will use the term OUD.

[5] The orphan-drug designation request at issue in this letter was submitted on May 5, 1993, and is subject to the orphan drug regulations that were in effect at the time. *See* 57 Fed. Reg. 62076 (Dec. 29, 1992). Accordingly, all

not considered, any additional information and arguments in the docket that were not relevant to the Agency's decision to revoke this orphan-drug designation.[6] Moreover, because the decision to revoke is grounded on a specific prong of the applicable regulation,[7] we have considered the information and arguments in the record only to the extent necessary to evaluate that regulatory basis for revocation.[8]

Indivior's orphan-drug designation for buprenorphine for treatment of "opiate addiction in opiate users" was predicated on a demonstration that there was "no reasonable expectation" that the cost of developing and making available in the United States (U.S.) buprenorphine for OUD could be recovered from sales in the U.S. of the drug.[9] The statute requires this determination to be made "on the basis of the facts and circumstances as of the date [of the orphan designation request]."[10] As explained in detail below, a reevaluation of the administrative record in light of the materials in this docket and additional relevant information has shown that FDA erroneously granted Indivior's orphan-drug designation request for buprenorphine for treatment of "opiate addiction in opiate users" because, on the basis of the facts and circumstances as of the date of the orphan designation request, it was unreasonable to conclude that there would be no cost recovery from sales of buprenorphine in the U.S.[11]

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citations in this letter are to the 1993 version of the regulations (the particular provision at issue has not changed substantively in the interim).

[6] Because FDA is revoking orphan-designation, Sublocade is not eligible for orphan-drug exclusivity. *See* 21 CFR § 316.29(b).

[7] 21 CFR § 316.29(a)(3).

[8] In other words, we did not need to evaluate information and arguments in the record to the extent they would support revocation under the other two prongs of the applicable regulation, i.e., 21 CFR § 316.29(a)(1) and/or (a)(2).

[9] *See* Section 526(a)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 360bb(a)(2)) (defining "rare disease or condition").

[10] *Id.*

[11] We are aware of another orphan-drug designation held by Indivior for buprenorphine with naloxone for "treatment of opiate addiction in opiate users." Because FDA granted the orphan-drug designation for buprenorphine with naloxone the same year and under a similar set of facts and circumstances as the designation for buprenorphine, we intend to reconsider whether the orphan-drug designation for buprenorphine with naloxone was also improperly granted.

I. Background

A. Legal Background

i. Orphan-Drug Designation

Congress enacted the Orphan Drug Act (ODA)[12] in 1983 to provide incentives for the development of drugs for rare diseases or conditions that would not otherwise be developed due to the small patient population and lack of profitability of such drugs. The ODA amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) by adding sections 525-528.[13] Section 526(a)(2) of the FD&C Act defines a "rare disease or condition" as any disease or condition that:

> (A) affects less than 200,000 persons in the U.S. ("the prevalence definition"), or
> (B) affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug. ("the cost recovery definition").

FDA's orphan drug regulations interpret the cost recovery definition to mean that a disease or condition is rare if there is no reasonable expectation that the sponsor can recover the costs of researching and developing the drug for the indication that is the subject of the request from sales of the drug in the U.S.[14] When a sponsor submits a cost recovery based orphan-drug designation request, FDA requires the sponsor to submit documentation, including authoritative references, regarding the expected cost of development of the drug and the expected revenue from sales of the drug for the first seven years of marketing.[15] For estimating cost, the documentation should include costs that the sponsor has incurred and expects to incur in the course of developing the drug for the U.S. market, and the expected production and marketing costs that the sponsor has incurred in the past and expects to incur during the first seven years that the drug is marketed.[16] The revenue estimate should take into account the expected total market for the drug, the estimated market share of the drug in each of the first seven years that it is marketed, and a projection for the price of the drug.[17] The estimates for the total market for the drug should equal the prevalence of the disease or condition that the drug will be used to treat.[18] As required by the statute, FDA determines eligibility for orphan-drug designation "on the basis of the facts and circumstances as of the date the request for designation of the drug…is made."[19]

Once designated, an orphan drug becomes eligible for certain incentives, including tax credits for qualified clinical testing, exemption from the application user fee, and, potentially, orphan-drug

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[12] Pub. L. No. 97-414, 96 Stat. 2049 (1983).
[13] Codified, as amended, at 21 U.S.C. §§ 360aa-dd. Throughout this response, "section" will refer to section of the FD&C Act, unless otherwise noted.
[14] 21 CFR § 316.20(b)(8)(ii).
[15] 21 CFR § 316.20(b)(8).
[16] 21 CFR § 316.21(c)(1)-(5).
[17] 21 CFR § 316.21(c)(6).
[18] *Id.*
[19] Section 526(a)(2) of the FD&C Act.

exclusivity. FDA's regulations at 21 C.F.R. Part 316 lay out the requirements for an orphan-drug designation request.[20]

ii. Revoking Orphan-Drug Designation

FDA's implementing regulations provide for revocation of orphan-drug designation at any time after a drug is designated as an orphan drug, if FDA finds that:

> (1) The request for designation contained an untrue statement of material fact [, or]
> (2) The request for designation omitted material information required by [the orphan drug regulations, or]
> (3) FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor.[21]

Accordingly, orphan-drug designation will be revoked if FDA determines, upon review, that the sponsor intentionally misled FDA or omitted material information, or, as relevant to this response, if the drug did not meet the eligibility criteria for designation at the time of the designation request. Revocation would be appropriate under the third prong if, for example, FDA later determined that information available at the time of the designation request was insufficient to establish the drug's eligibility for designation because the Agency was not aware of, or did not consider, information necessary to properly evaluate whether the drug met the designation standard.[22]

The regulations also state that FDA will not revoke an orphan-drug designation if the designation was based on the prevalence of the disease or condition being under 200,000, but the prevalence later becomes more than 200,000.[23] FDA will also not revoke a cost recovery based orphan-drug designation solely because the drug has become profitable. This latter principle is not explicitly stated in the regulation, however, in the preamble to the 1992 final regulation, FDA rejected a comment that suggested "orphan-drug designation and exclusive marketing should be revoked when FDA determines that a drug that it has designated is later proved to have commercial potential" because "legislation that would have authorized FDA to take such actions was vetoed by the President in 1990."[24]

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[20] *See* 21 CFR § 316.20-21.

[21] 21 CFR § 316.29(a).

[22] You point to FDA's review of the orphan-drug designation for Evista to state that FDA can revoke orphan-drug designation based on new information demonstrating that the drug product actually is profitable and thus that the initial economic assumptions were not reasonable. FDA has never revoked a cost recovery based orphan-drug designation because new information demonstrated that a drug that met the cost recovery prong at the time of the designation request later became profitable. However, FDA may revoke a cost recovery orphan-drug designation if new information demonstrates that the drug did not meet the cost recovery standard at the time of the designation request. For example, such new information can show that the economic assumptions underlying the Agency's analysis at that time were erroneous or were not reasonable.

[23] 21 CFR § 316.29(c). This is consistent with the statutory requirement that FDA evaluate a designation request "on the basis of the facts and circumstances as of the date the request for designation of the drug . . . is made." Section 526(a)(2).

[24] 57 Fed. Reg. 62076, 62082 (Dec. 29, 1992).

B. Procedural Background

On May 5, 1993, Indivior requested orphan-drug designation for buprenorphine for "treatment-seeking opiate users in opiate detoxification and maintenance treatment schedules" under the prevalence definition of a rare disease.[25] Indivior claimed that buprenorphine may be used as an alternative treatment modality for treatment-seeking opioid users who may otherwise enter a methadone maintenance program, and therefore the number of patients enrolled in methadone programs would represent the upper bound of potential buprenorphine patients.[26] Indivior stated that at the time about 115,000 patients were enrolled in methadone maintenance programs.[27]

Upon review of the original request for orphan-drug designation, FDA determined that buprenorphine was not eligible for designation because Indivior did not establish that the disease or condition (in this case, OUD) had a prevalence below 200,000.[28] FDA found that most sources at the time estimated the number of opioid addicts to be between 1,000,000 and 1,500,000.[29] As FDA explained to Indivior, to evaluate orphan-drug designation requests based on the prevalence definition of a rare disease, FDA estimates prevalence based on the number of patients diagnosed with the disease, not only those that are likely to seek or receive treatment.[30] While FDA may designate a drug for an orphan subset of a non-rare disease if the subset is medically plausible,[31] there is no property of buprenorphine that would limit its use to the number of addicts that are "treatment-seeking," nor to the number of addicts that are currently on drug therapy and likely to use a pharmacologic agent.[32] In addition, FDA noted that Indivior insufficiently justified how many addicts are "treatment-seeking," because it did not provide the number of patients in programs other than methadone maintenance clinics.[33] FDA concluded that the prevalence of the disease exceeded the 200,000 person threshold and Indivior's buprenorphine was ineligible for orphan-drug designation for treatment of OUD.[34]

On July 14, 1993, FDA met with representatives from Indivior to discuss the request for orphan-drug designation.[35] At the meeting, FDA explained that it found the prevalence of OUD to be over 200,000 and recommended that Indivior amend its request for orphan-drug designation with financial information and seek orphan-drug designation based on the cost recovery definition of

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[25] *Indivior*, Request for orphan drug designation for buprenorphine, p. 2 (May 5, 1993) ("Indivior request") *in Hyman, Phelps & McNamara, PC for Indivior*, Comment to Docket No. FDA-2019-P-1679, Exhibit D (July 24, 2019) *available at* https://www.regulations.gov/document?D=FDA-2019-P-1679-0071 ("Indivior July Comment").
[26] *Id.* at 7.
[27] *Id.* at 7-8 (citing *FDA Talk Paper T93-5*, Interim Methadone Maintenance Regulations, Jan. 14, 1993).
[28] *FDA*, Review of request for orphan drug designation for buprenorphine, p. 3 (June 25, 1993) (Exhibit 3 in Docket) ("Designation review").
[29] *Id.*
[30] *See* 21 CFR § 316.21(b). *See also* Designation review, *supra* note 28 at 3 ("The law specifically uses the words disease or condition, and does not mention those who are likely to use the product or seek treatment; therefore it would seem reasonable to assume that if there are 1,000,000 opioid addicts then the disease or condition which this drug is intended to treat contains a population of 1,000,000 patients.").
[31] *See* 316.20(b)(6).
[32] Designation review, *supra* note 28 at 3.
[33] *Id.*
[34] *Id.*
[35] *FDA*, *Memorandum of Meeting* (July 14, 1993) *in* Indivior July Comment, *supra* note 25, Exhibit G.

rare disease.[36] Following the meeting, on August 20, 1993, FDA formally responded to the request for orphan-drug designation by sending Indivior a deficiency letter stating that review of the designation request was being held in abeyance pending the receipt of additional information.[37] In the letter, FDA explained why it was unable to accept Indivior's prevalence estimate and that if Indivior wanted to continue to pursue orphan-drug designation for buprenorphine for OUD under the prevalence definition of rare disease or condition, Indivior would need to provide a justification for designation of an orphan subset. FDA suggested, alternatively, that Indivior request orphan-drug designation under the cost recovery definition of rare disease or condition.

On November 15, 1993, Indivior submitted an amendment to its request for orphan-drug designation to establish that buprenorphine for OUD qualifies for orphan-drug designation under the cost recovery definition.[38] To estimate the expected revenue from sales during the first seven years of marketing, Indivior relied on the following assumptions: (1) The "current maximum population eligible for treatment of addiction with any narcotic is limited to 115,000 patients," and it was unlikely the relevant laws would change during the life of the product; (2) Due to roughly 10 percent of treatment slots going unfilled at any given time, the available patient population was 104,000; (3) Due to the partial agonist properties of buprenorphine, it cannot equate to the higher dosage levels of methadone and would not be suitable for many of those 104,000 patients; and (4) In order to compete with methadone and levomethadyl acetate (LAAM) (another opioid product expected to be used for treating OUD), Indivior claimed it would need to set a competitive price or otherwise it would need to proportionally reduce the anticipated market penetration.[39] Indivior used these assumptions to estimate the total market, market share, and price per dose, which all formed the basis for the sales estimate.

Indivior did not provide a citation to support its assertion that the number of methadone treatment slots was limited to 115,000 and would be unlikely to change. The 115,000 number is the same that Indivior provided in its initial request for designation as the number of patients "currently enrolled in methadone programs," which does not appear to be a number set by regulation.[40] Instead, this number seems consistent with data from surveys conducted around that time, such as a 1990 survey that estimated 112,943 patients received methadone and a 1993 survey that found an estimated 117,000 patients received methadone.[41] On the other hand, according to the National Drug and Alcoholism Treatment Unit Survey, the number of patients being treated with methadone grew by 27.6 percent between 1987 and 1992.[42]

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[36] *Id.*

[37] Letter from Marlene Haffner to Charles O'Keeffe, *Deficiency Letter* (August 20, 1993) *in* Indivior July Comment, *supra* note 25, Exhibit F.

[38] *Indivior*, Amendment to request for orphan drug designation for buprenorphine, p. 2 (November 15, 1993) (Exhibit 16 in Docket) ("Amendment request").

[39] *Id.*

[40] Indivior request, *supra* note 25 at 7.

[41] Institute of Medicine (US) Committee on Federal Regulation of Methadone Treatment, Rettig RA, Yarmolinsky A, editors, *Federal Regulation of Methadone Treatment*, Washington (DC): National Academies Press (US); 1995. 6, Methadone Treatment, available at: https://www.ncbi.nlm.nih.gov/books/NBK232107/?report=classic ("IOM article").

[42] *Id.*

The "regulations" mentioned by Indivior are likely a reference to the 1972 FDA regulations[43] (amended in 1980[44] and 1989[45]) that, along with the Narcotic Addict Treatment Act (NATA) of 1974, established a highly regulated system of methadone treatment programs. Specifically, FDA's regulations allowed methadone treatment only in "methadone treatment programs" and "methadone treatment medication units" that were approved by both the FDA and the relevant state agency. Conditions of approval included providing services, such as counseling and rehabilitation, and being within a hospital or having an agreement with a hospital to provide inpatient or outpatient care to any patient needing it. Methadone treatment medication units were limited to treating 30 patients. The regulation also distinguished between detoxification and maintenance therapy and provided requirements for minimum dosage, dose adjustments and observation of medication taking. In sum, the regulations restricted access to methadone treatment to approved facilities and controlled the number of patients these facilities could treat, but did not set a cap on the number patients nationwide who could access methadone treatment.

To estimate the expected costs of development, Indivior included information about preclinical and clinical studies, but did not include a "wide range of items which could be considered under the regulations" because "of the difficulty of adequately itemizing and allocating" these costs.[46] Nevertheless, Indivior stated that it had established that it would be unable to recover its costs even without including all of the costs it potentially could have.[47] As required by 21 CFR §316.21(c)(8), Indivior included a report of an independent certified public accountant. The report stated that the cost recovery calculations were compiled on the basis of the "assumptions made by the company" and were "consistent with the generally accepted accounting principles and policies adopted by" Indivior.[48]

FDA reviewed Indivior's cost recovery analysis to determine if there was no reasonable expectation that the cost of developing and making available in the U.S. buprenorphine for OUD would be recovered from sales in the first seven years of marketing of the drug.[49] FDA acknowledged that Indivior based its amended request for designation on several assumptions, including that the maximum number of treatment-seeking patients was limited to 104,000, and that there would be virtually no change in the numbers of treatment-seeking patients during the first seven years of marketing of the drug.[50]

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[43] FDA, Approved New Drugs Requiring Continuation of Long-Term Studies, Records, and Reports; Listing of Methadone with Special Requirements for Use, Final Rule, 37 Fed. Reg. 26790 (Dec. 15, 1972).
[44] FDA, Joint Revision of Conditions for Use of Methadone for Treating Narcotic Addicts, Final Rule, 45 Fed. Reg. 62694 (Sep. 19, 1980).
[45] FDA, National Institute on Drug Abuse; Methadone in Maintenance and Detoxification; Joint Revision of Conditions for Use, Final Rule, 54 Fed. Reg. 8954 (Mar. 2, 1989).
[46] Amendment request, *supra* note 38 at 3.
[47] *Id.*
[48] Letter from accountant to Reckitt & Colman (November 11, 1993) (Enclosure 1).
[49] *FDA*, Review of amendment to request for orphan drug designation for buprenorphine (June 14, 1994) (Exhibit 4 in Docket) ("Amendment review").
[50] *Id.* at 5.

Using the assumptions and figures provided by Indivior, FDA produced a sensitivity analysis to account for "additional hypotheses that might affect the first 7 years of marketing results."[51] The results of this analysis appear in FDA's review as several charts outlining different scenarios. Specifically, the different scenarios calculated the net loss or net profit for the first seven years of marketing based on (1) whether there would be a 0-3 year delay in marketing the drug, (2) whether the patient population that switches from methadone to buprenorphine would be the same as estimated by Indivior, 50% more, or 100% more, and (3) whether the sales price would be the same as estimated by Indivior, or increased by $1. Notably, in four out of nine scenarios, FDA's analysis indicated that buprenorphine would provide a positive return on investment following the first seven years of sales in the U.S.[52] The chart below summarizes each scenario and whether the result indicated a net loss or net profit for buprenorphine in the first seven years of marketing.

[51] *Id.* at 4.
[52] *Id.* at 4-5.

Scenario Note: Scenario 1 represents Indivior's assumptions. Italics indicate a change from Indivior's assumptions in scenario 1.		Net loss or net profit for buprenorphine in the first seven years of marketing
1	1. Buprenorphine approved and marketed in 1995 2. Market share as estimated by Indivior 3. Sales price as estimated by Indivior	Loss
2	1. *Marketing delayed two years later than scenario 1* 2. Market share as estimated by Indivior 3. Sales price as estimated by Indivior	Loss
2A	1. *Marketing delayed three years later than scenario 1* 2. Market share as estimated by Indivior 3. Sales price as estimated by Indivior	Loss
3A	1. Buprenorphine approved and marketed in 1995 2. *50% more patients switch from methadone to buprenorphine than scenario 1* 3. Sales price as estimated by Indivior	Profit
3B	1. *Marketing delayed two years after approval* 2. *50% more patients switch from methadone to buprenorphine than scenario 1* 3. Sales price as estimated by Indivior	Loss
4	1. Buprenorphine approved and marketed in 1995 2. *100% more patients switch from methadone to buprenorphine than scenario 1* 3. Sales price as estimated by Indivior	Profit
4A	1. *Marketing delayed two years later than scenario 1* 2. *100% more patients switch from methadone to buprenorphine than scenario 1* 3. Sales price as estimated by Indivior	Loss
6	1. Buprenorphine approved and marketed in 1995 2. *100% more patients switch from methadone to buprenorphine than scenario 1* 3. *Sales price $1 more per dose than scenario 1*	Profit
6A	1. *Marketing delayed two years later than scenario 1* 2. *100% more patients switch from methadone to buprenorphine than scenario 1* 3. *Sales price $1 more per dose than scenario 1*	Profit

This analysis demonstrated that there were scenarios under which FDA could potentially expect Indivior to recover the cost of developing and making available buprenorphine in the U.S. through sales. At the same time, FDA considered whether the assumptions underlying scenario 1 (the baseline scenario presented by Indivior) were reasonable and determined that they were.[53] FDA agreed with Indivior that, because opioid products for treating OUD were purchased by

[53] *Id.* at 6 ("This reviewer concludes that the patient population estimates and market share submitted by the sponsor are reasonable and fair").

treatment centers or governments rather than individuals, it was reasonably unlikely that buprenorphine would supplant the market for cheaper products, such as methadone and LAAM, and Indivior would be unlikely to charge a standard markup for a new indication.[54] FDA also agreed it was "reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift would be incremental."[55] FDA's review does not state why that assumption was reasonable. Similarly, the record does not indicate whether the Agency considered the possibility that total market size could increase, for example if the laws restricting access to opioids for treatment of OUD were to change to allow greater access to such drugs. FDA's review also does not address the hypothetical scenarios that showed a positive return on investment for buprenorphine, or explain how they fit into the "no reasonable expectation" for profit framework set out by the ODA. Nevertheless, the Agency concluded that there was "no reasonable expectation that the development costs will [be] recovered in the first 7 years of marketing,"[56] and granted orphan-drug designation to Indivior for buprenorphine for the treatment of "opiate addiction in opiate users."[57]

On October 8, 2002, FDA approved Indivior's marketing application for Subutex (buprenorphine) sublingual tablets for treatment of opioid dependence in patients 16 years of age or older. FDA also recognized orphan-drug exclusivity for Subutex from October 8, 2002, until October 8, 2009.

Subsequently, Indivior submitted a new drug application for Sublocade, an extended-release injection of buprenorphine for the treatment of moderate to severe opioid use disorder. On November 30, 2017, FDA approved Indivior's marketing application for Sublocade. At the time this Citizen Petition was submitted, FDA's assessment of whether Sublocade is eligible for orphan-drug exclusivity was pending. Because FDA is revoking Indivior's orphan-drug designation for buprenorphine, Sublocade will not be eligible for orphan-drug exclusivity. Accordingly, at this time, FDA need not address the additional arguments in the docket regarding Sublocade's eligibility for orphan-drug exclusivity.

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[54] *Id.* at 5.
[55] *Id.*
[56] *Id.* at p. 6.
[57] Letter from Marlene Haffner to Charles O'Keeffe, *Orphan drug designation letter* (June 15, 1994) (Exhibit 2 in Docket) ("Buprenorphine designation letter").

II. Discussion

You have asked FDA to revoke Indivior's cost recovery based orphan-drug designation for buprenorphine for treatment of "opiate addiction in opiate users." This matter of first impression requires that we determine whether orphan-drug designation was appropriately granted pursuant to the cost recovery definition. Under that definition, FDA must evaluate, as of the time the designation request was submitted, whether a sponsor is able to establish that "there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for [a non-rare] disease or condition will be recovered from sales in the U.S. of such drug."[58] Thus, when considering the revocation of Indivior's orphan-drug designation for buprenorphine, the plain text of the statute requires that we evaluate whether the assumptions underlying our decision that buprenorphine met the designation standard were reasonable at the time of the designation request.[59] FDA may revoke the orphan-drug designation if the assumptions underlying the decision that buprenorphine met the cost recovery definition of a rare disease were not reasonable at the time of the designation request. The "no reasonable expectation" inquiry also involves an evaluation of, among other things, whether FDA had sufficient information to determine if buprenorphine met the cost recovery definition.

After a careful review of the Docket submissions and Indivior's 1993 request for orphan-drug designation and other relevant information, we have determined that the request for orphan-drug designation failed to establish that there was no reasonable expectation that the costs of developing a buprenorphine drug to treat OUD would be recovered from the sales of such a drug in the U.S. We reach this conclusion for two independent reasons: (1) For purposes of the cost recovery analysis, it was not reasonable to assume that the market size would remain constant for the first seven years of marketing of buprenorphine for OUD, because, for example, it was not reasonable to assume that the laws restricting access to treatment of OUD with opioids were unlikely to change during the relevant timeframe, or because it was not reasonable to assume the number of treatment facilities would not increase, and (2) The cost recovery analysis did not account for buprenorphine products (including particular formulations and dosage forms) other than the sublingual tablet in estimating potential costs and revenue, and therefore FDA did not have the information necessary for the Agency to properly evaluate the designation request. Thus, buprenorphine was not eligible for orphan-drug designation for treatment of "opiate addiction in opiate users" at the time of designation.

A. For purposes of the cost recovery analysis, it was not reasonable to assume that the market size would remain constant for the first seven years of marketing of buprenorphine for OUD

In order to establish that there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for a disease or condition will be recovered from sales in the U.S. of such drug, a sponsor is required to produce, among other things, an estimate of sales in the U.S. of the drug for the disease or condition.[60] The sales figure is based on an estimate of the

[58] Section 526(a)(2)(B) of the FD&C Act.
[59] *Id.*
[60] 21 CFR § 316.21(c)(6).

total market size for the drug, an estimate of the share of that market the drug will penetrate, and an estimate of the price of the drug.[61] These estimates are in turn based on certain underlying assumptions. The assumption that the total market for buprenorphine would be limited to 104,000 patients (of the estimated 1 to 1.5 million patients with OUD at the time) throughout the first seven year marketing period of the drug in the U.S was fundamental to the analysis in this instance.[62] Indivior provided that number as the total market for buprenorphine because, it explained, the relevant laws at the time of the designation request limited access to treatment of OUD with opioids to 115,000 patients per day, and only 104,000 patients filled those slots at any given time.[63] Another, closely-linked assumption was that the relevant laws restricting access to treatment of OUD with opioids were unlikely to change during the first seven years of marketing period of the drug. As explained below, neither of these were reasonable assumptions at that time. Not only was it conceivable at the time of designation that the laws could change in the future and allow significant additional patient access to buprenorphine, but there is also no evidence that the total number of treatment facilities would remain constant. Thus, it was not reasonable to assume that market size would remain constant for the first seven years of marketing of buprenorphine for OUD.

i. It was not reasonable to assume that the market size would remain constant for the first seven years of marketing of buprenorphine for OUD

Analysis of the issues raised in the Petition requires that we first assess whether - at the time of the designation request - it was reasonable to expect that the market size would remain constant for the first seven years of marketing of buprenorphine for OUD, either because the applicable laws restricting the use of buprenorphine would not change throughout the first seven years of the drug's marketing, or because the number of treatment facilities would not increase. After reviewing the record and other available information, we conclude that this was not a reasonable assumption. We recognize that this is a complex question that involves multiple factors. It requires that we evaluate how the agency should have analyzed the impact of a complicated regulatory framework that was applicable to a specific set of products more than 20 years ago, and that has since undergone significant change. Not surprisingly, the docket comments from Braeburn and Indivior construe the facts in diametrically opposed ways to support different outcomes. Nevertheless, we must analyze these factors in light of the facts applicable at the time of designation in order to decide a key request in the Petition. Fortunately, we are aided in our analysis because we have access to a comprehensive and detailed account that explains the "facts and circumstances" applicable to this designation during the appropriate timeframe.[64] This account, co-authored by Charles O'Keeffe, former president and CEO of Indivior, also includes

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[61] *Id.*

[62] FDA's cost recovery analysis utilized other assumptions provided by Indivior, including the timing of approval and marketing of buprenorphine, the market share buprenorphine would acquire, and the price per dose of buprenorphine Indivior could charge. FDA did not reevaluate the appropriateness of each of these assumptions and only focuses here on the assumption that the relevant laws regulating access to treatment of OUD with any opioid would not change.

[63] Amendment request, *supra* note 38 at 2.

[64] J. Jaffe, C. O'Keeffe, *From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States*, Drug and Alcohol Dependence, 70: S3-S11 (2003) ("O'Keeffe Article") (Exhibit 17).

crucial insight into Indivior's perspective and internal thinking at the time of the designation request because Mr. O'Keeffe was Executive Vice President at the time Indivior requested orphan-drug designation for buprenorphine and signed the buprenorphine orphan-drug designation request.[65]

As the O'Keeffe article accurately explains, at the time of the request for designation, "the regulatory framework dealing with the use of opioids in the treatment of addiction in the U.S …consisted of a dual oversight at the federal level (HHS and DEA), as well as various (and varying) regulatory requirements at the state and local levels."[66] The 1972 FDA regulations[67] controlling the conditions of use for methadone and the Narcotic Treatment Act of 1974 (NATA)[68] established a complex system where treatment of OUD with methadone was highly regulated and restricted to certain treatment facilities. As explained above, the 1972 regulations allowed methadone treatment only in "methadone treatment programs" and "methadone treatment medication units" that were approved both by FDA and the relevant state agency. The regulations controlled many aspects of treatment, such as dosages to be used and the amount of counseling that must be provided, and limited the number of patients that could be treated at each methadone treatment medication unit. Thus, there was tight control over the facilities that provide methadone treatment, and the number of patients for whom treatment of OUD with methadone would be available was dependent on the number of approved facilities at any given time.

In the designation request, Indivior stated that the limitation on the number of methadone treatment slots "and the regulations establishing it are highly unlikely to be modified during the life of the product."[69] Indivior did not provide any evidence to support that the number of methadone treatment slots was unlikely to change, nor did it explain why the regulations were unlikely to be modified during the life of the product. FDA accepted these assumptions without further analysis.[70] FDA's review stated, "It is reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift will be incremental. Thus, over seven years, the additional patients on this product beyond those projected by the sponsor should be inconsequential economically on the results of this analysis."[71] Upon reevaluation, we have now determined that this conclusion was erroneous at the time it was made.

It was not reasonable to assume at the time of the designation request that the relevant laws restricting access to treatment of OUD with opioids that were in place at that time would not be revised to address the different risk profiles represented by partial agonists like buprenorphine. First, applicable statutes and regulations were written in the context of drugs like methadone and LAAM, which had high potential for abuse and diversion. The regulatory framework was established to minimize diversion of opioid drugs from treatment programs due to the "serious

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[65] *See* Indivior Request, *supra* note 25 at 8; Amendment Request, *supra* note 38 at 3.
[66] O'Keeffe Article, *supra* note 64 at S6. *See also* IOM article, *supra* note 41.
[67] FDA, Approved New Drugs Requiring Continuation of Long-Term Studies, Records, and Reports; Listing of Methadone with Special Requirements for Use, Final Rule, 37 Fed. Reg. 26790 (Dec. 15, 1972).
[68] Pub. L. No. 93-281, 88 Stat. 124 (1974).
[69] Amendment request, *supra* note 38 at 3.
[70] Amendment review, *supra* note 49 at 5.
[71] *Id.*

toxic consequences that ensue when non-tolerant individuals ingest dosages of methadone or LAAM typically used in treatment."[72] But buprenorphine has qualities that distinguish it from these products and those qualities were fairly well understood at the time the request for designation was submitted. Though less was known about buprenorphine at the time the relevant laws were drafted, by the early 1990s, when the designation request was submitted, there was evidence that, compared to methadone and LAAM, buprenorphine, as a partial agonist, could be used for treatment of OUD with potentially less toxicity even for non-tolerant individuals.[73] Indeed, Indivior itself cited the potential benefits of buprenorphine in its request for orphan-drug designation. According to Indivior, "buprenorphine is a partial agonist with low dependence liability and toxicity and has been extensively used as an analgesic agent since the late 1970's . . . . It is the ceiling on its agonist effects that accounts for buprenorphine's remarkable safety and lack of toxicity."[74] Thus, it would have been unreasonable not to recognize that buprenorphine is materially different from methadone in a way that would potentially support a different regulatory approach.

The 1982 scheduling of buprenorphine for pain serves as another example of existing information that buprenorphine differed from other opioids used for addiction treatment. When FDA approved buprenorphine for pain, HHS recommended that DEA reschedule the drug from Schedule II to Schedule V "based on findings that buprenorphine has a low potential for abuse relative to the drugs or other substances in Schedule IV...and that abuse of buprenorphine may lead to limited physical dependence or psychological dependence relative to other drugs or other substances in Schedule IV."[75] At the time, Indivior argued that buprenorphine should not even be a controlled substance because buprenorphine "does not possess sufficient potential for abuse to justify control."[76] Ultimately, the DEA agreed to place buprenorphine in Schedule V based on the reasons presented by HHS.[77]

Given Indivior's position that buprenorphine had "remarkable safety and lack of toxicity," as well as the 1982 scheduling analysis, it was unreasonable for FDA to assume that the laws and regulations applicable to other opioids which possessed significantly different qualities, and which were designed to minimize opportunities for abuse of those abuse-prone substances, would continue to apply equally to buprenorphine during the relevant time period.

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[72] O'Keeffe article, *supra* note 64 at S7.

[73] *Id. See also* Jasinski DR, Pevnick JS, Griffith JD, *Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction*, Arch Gen Psychiatry. 35(4):501-16 (Apr 1978) ("The drug was morphine-like but was 25 to 50 times more potent than morphine and was longer-acting. Little if any physical dependence of clinical significance was produced by buprenorphine.").

[74] Indivior request, *supra* note 25 at 2.

[75] DEA, Schedules of Controlled Substances; Proposed Rescheduling of Buprenorphine From Schedule II to Schedule V of the Controlled Substances Act, Notice of proposed rulemaking, 47 Fed. Reg. 41401 (September 20, 1982).

[76] DEA, Controlled Substances; Buprenorphine, Notice of hearing on proposed rulemaking, 48 Fed. Reg. 19037 (April 27, 1983).

[77] DEA, Schedules of Controlled Substances; Rescheduling of Buprenorphine From Schedule II to Schedule V of the Controlled Substances Act, Finale rule, 50 Fed. Reg. 8104 (February 28, 1985).

Second, the applicable laws were drafted with the intention that they would eventually be revised, and there was already public discussion of changing the regulatory framework at the time of the designation request. The drafters of the 1972 regulation in the White House Special Action Office for Drug Abuse Prevention (SAODAP) "did not intend for medication dispensing to be forever limited to a few large clinics."[78] Although the regulations established a strict system under which patients could access treatment, the drafters "believed that the regulations would be revised as knowledge expanded and as opioid maintenance treatment became less controversial."[79] The regulations were even written in anticipation of "a time when clinics and individual practitioners would be linked to pharmacies and other sites that would be authorized to dispense drugs," as opposed to restricting patients to highly regulated treatment facilities.[80] Beyond the drafters of the regulation, "clinicians . . . criticized the Federal regulations as a burdensome interference with the practice of medicine."[81] It was therefore unreasonable to assume at the time of the request for designation that the regulatory framework would not be updated. In fact, by the time Indivior submitted its request for designation in 1993, the 1972 regulations had been updated twice. The 1980 and 1989 revisions to the regulation did not fundamentally change the structure for methadone treatment, but did provide for numerous changes. The 1980 revisions included a reduction in the minimum standard for admission, changed the limit on the initial dose, and restricted take-home methadone to a liquid form for "responsible" patients.[82] The 1989 revisions included reclassification of detoxification into short- and long-term, deletion of a specific counselor-patient ratio, and allowance of procedures other than urinalysis to test for illicit drugs.[83] Although these changes did not significantly alter the framework of methadone treatment, they did signify that the regulations were evolving over time, and would likely continue to evolve, especially if additional opioid products were approved to treat OUD.

Congress itself signaled a willingness to change the laws when it commissioned a report from the Institute of Medicine (IOM).[84] In the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) Reorganization Act of 1992,[85] Congress called for a study concerning anti-addiction medications, including "legislative proposals designed to encourage private sector development of such medications" and "recommendations with respect to a national strategy for developing such treatments and improvements in such strategy."[86] The results of the IOM report were not published at the time Indivior requested designation, but in passing ADAMHA, Congress indicated in 1992 that it was actively looking for legislative proposals to amend the

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[78] O'Keeffe article, *supra* note 64 at S5. The article's coauthor Jerome H. Jaffe was the director of SAODAP, which worked with FDA to write the 1972 regulations. *See also* Jaffe, J.H., *The maintenance option and the Special Action Office for Drug Abuse Prevention*, Psychiatr. Ann. 5, 12-42 (1975).

[79] *Id.*

[80] *Id.*

[81] *Id.*

[82] FDA, Joint Revision of Conditions for Use of Methadone for Treating Narcotic Addicts, Final Rule, 45 Fed. Reg. 62694 (Sep. 19, 1980).

[83] FDA, National Institute on Drug Abuse; Methadone in Maintenance and Detoxification; Joint Revision of Conditions for Use, Final Rule, 54 Fed. Reg. 8954 (Mar. 2, 1989).

[84] *See* Institute of Medicine, The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector (1995), available at: http://www.nap.edu/catalog/4906.html.

[85] Pub. L. No. 102-321, 106 Stat. 323 (1992).

[86] *Id.* at Sec. 701(a).

laws regarding opioid treatment.[87] IOM did make such recommendations, including "expanding the treatment capabilities of the states for opiate-and cocaine-dependent individuals to ensure that all those seeking treatment obtain it without delay."[88] This could be achieved by "[p]roviding additional money to increase treatment in states where there are waiting lists."[89] These conclusions were based on information available at the time of the designation request and were the type of conclusions that should have been reasonably foreseeable when Congress commissioned the study in 1992.

Third, when Indivior requested orphan-drug designation for buprenorphine, it had already considered the possibility that the regulatory framework would change to expand the market for buprenorphine, and factored the benefit of such a potential change into its business plan.[90] The O'Keeffe article outlines Indivior's plan regarding the marketing of buprenorphine for OUD: obtain orphan-drug designation, change the laws to increase the size of the market, and obtain marketing approval.[91] Indivior believed that updates to the regulatory framework were necessary to expand the market, and obtaining orphan-drug designation was necessary to monopolize that market after approval.

> [F]rom the perspective of [Indivior], . . . the legislative effort to [expand the buprenorphine market] and the effort to develop and win FDA approval for its use in addiction treatment were seen as being inextricably intertwined. . . . Also, from a corporate perspective, it seemed unlikely that a drug confined to a limited number of clinics that were already comfortable using generic methadone would be used enough to justify the investment involved in taking buprenorphine through the regulatory process.[92]

The Board of Directors for Indivior appears to have decided, at the time of the designation request, to approve the development plan based on the possibility that Indivior could accomplish those goals.[93] Based on the events described, it seems clear that Indivior would not have sought orphan-drug designation and marketing approval for buprenorphine for treatment of OUD unless it also had a reasonable expectation of expanding the market for buprenorphine. Although a change in the law was far from assured, Indivior's Board seems to have believed that there was a reasonable expectation that such a change would occur.

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[87] *Id.*
[88] Institute of Medicine, *supra* note 84 at 116.
[89] *Id.*
[90] Indivior argues that their lobbying efforts are not "material information required" by 21 CFR § 316.29(a)(2). *See* Indivior July Comment, *supra* note 25 at 15. FDA has not determined whether Indivior's lobbying efforts are material information required by 21 CFR § 316.29(a)(2), nor if Indivior "omitted" such material information under 21 CFR § 316.29(a)(1). The discussion of Indivior's lobbying efforts in this part are limited to the purpose of establishing that it was not reasonable to assume that the relevant laws restricting access to opioids for treatment of OUD would not change.
[91] O'Keeffe article, *supra* note 64 at S7-S8.
[92] *Id.* at S7.
[93] *Id.*

> [Indivior] knew it would be at least a 5-year project and that it would be committing millions of dollars to develop a product that had no patent protection remaining. The Board of Directors decided to approve the process nevertheless.[94]

In addition, as explained above, even if the regulatory framework remained unchanged during the first seven years of marketing of buprenoprhine, it did not limit the total number of treatment facilities. Indeed, that number had already increased by a significant amount in the time period just prior to the designation request.[95] Accordingly, it seems reasonable to conclude that Indivior's Board would not have agreed to the development plan for the drug if the company had no reasonable expectation that the market size for buprenorphine would expand.

ii. Indivior's assertions and arguments with respect to the orphan-drug designation for buprenorphine do not change our conclusion

Indivior submitted two comments to the docket, arguing, among other things, that the designation of buprenorphine was proper.[96] First, Indivior asserts that the predictions it made in 1993 about the future earning potential of buprenorphine cannot be a basis to revoke orphan-drug designation, because these predictions are not "facts" within the meaning of 21 CFR §§ 316.29(a)(1) & (2).[97] This comment is not relevant since our decision is not based on the first two prongs of 21 CFR § 316.29(a). Instead, our conclusion rests solely on an analysis of whether buprenorphine was in fact eligible for orphan-drug designation for treatment of OUD at the time of submission of the request for orphan-drug designation under 21 CFR § 316.29(a)(3). As discussed above, this evaluation requires FDA to determine if the assumptions used for the cost recovery analysis were reasonable at the time of the designation request.

Next, Indivior argues that its assumption that buprenorphine would be approved in 1995 is not a basis for rescinding the orphan-drug designation.[98] The assumption about when buprenorphine would be approved for treatment of OUD is relevant to the finding that it was not reasonable to assume that the relevant laws restricting access to treatment of OUD with opioids would not change. This is because the cost recovery analysis uses sales information from the first seven years of marketing, so an assumption about when the drug would be approved and marketed relative to when the laws would change is material to the cost recovery analysis. Indivior rightly points out that FDA included a potential delay in approval and marketing in its cost recovery analysis.[99] However, FDA's analysis did not factor in the possibility of the laws restricting access to treatment changing before or during the first seven years of marketing, and therefore the analysis was insufficient to determine if there were no reasonable expectation that sales of buprenorphine would recover Indivior's costs during the first seven years of marketing. Even using the assumption provided by Indivior that buprenorphine would be approved and marketed

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[94] *Id.*

[95] *See supra* notes 41-42.

[96] *See* Indivior July comment, *supra* note 25; *Hyman, Phelps & McNamara, PC for Indivior*, Comment to Docket No. FDA-2019-P-1679 (Oct. 1, 2019) *available at* https://www.regulations.gov/document?D=FDA-2019-P-1679-0076.

[97] Indivior July comment, *supra* note 25 at 15.

[98] *Id.* at 16-17.

[99] *Id.*

in 1995, which incidentally seems to have been an optimistic timeline even at the time of designation,[100] the cost recovery analysis would have to account for sales through 2002. As explained above, it was not reasonable to assume that the relevant laws restricting access to treatment of OUD with opioids would not change during the entirety of the time period from 1995 to 2002. In particular, the regulations would likely have had to been updated after buprenorphine was approved for treatment of OUD. Even if the laws were to change in the sixth year of marketing, it is possible that just one year of sales under different restrictions would result in a return on investment for buprenorphine. In addition, increases in the number of treatment facilities during the relevant time frame could reasonably have resulted in a profit, but FDA's analysis does not seem to have explicitly considered this factor. As discussed below, to the extent that the various scenarios did consider increases in market share for buprenorphine as surrogates for such changes in market size, those scenarios resulted in a profit.

Indivior points out that at the time the request for designation was submitted, the relevant regulations had been revised only twice, those changes were relatively minor, and even limited reform proposals had faced stiff resistance.[101] This argument is not dispositive, however, because past difficulty in and resistance to changing the relevant laws is not necessarily indicative of the likelihood of future chances of updating the regulatory framework. As explained above, and as Indivior also emphasized, buprenorphine has qualities that materially distinguish it from the products that were previously on the market and for which the regulatory framework existing at the time was created. While the difficulties in changing the regulatory framework does inform the reasonableness analysis, in light of the discussion above, this fact, standing alone, does not establish that it was reasonable for FDA to assume that the regulatory *status quo* would continue to prevail for the next seven years.

Indivior also suggests that the length of time it actually took to modify the relevant laws restricting access to treatment of OUD with opioids retroactively justifies its assumption that these laws were unlikely to change.[102] Indivior states that the time it took to achieve these reforms "substantiates both the accuracy and reasonableness" of its prediction that changing the laws "faced long odds."[103] First, as stated above, FDA's determination regarding the request for designation is based on the facts and circumstances available at the time of the request for designation. Second, even assuming that it would be appropriate to superimpose the actual course of events onto the Agency's assumptions at the time of designation, Indivior's assertion cuts both ways. The applicable statutes did change in 2000, expanding the market for

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[100] FDA concluded in 1994 that "it seems reasonable to conclude that marketing approval is at least two or more years away," Amendment Review, *supra* note 49 at 4. Also, FDA often grants orphan-drug designation many years before a drug is approved. Sponsors may (and do) seek marketing approval decades after receiving orphan-drug designation for their orphan drugs.

[101] Indivior July Comment, *supra* note 25 at 18.

[102] *Id.* at 19 ("...the regulatory reform efforts first advocated by IOM in 1995 were not implemented until 2001...some eight years after [Indivior] correctly predicted in 1993 that meaningful regulatory reform was 'highly unlikely.'").

[103] *Id.* If Indivior believes that the length of time it took to change the laws substantiates its assumption that changing the laws was unlikely, it seems that we would also have to assume that it was unreasonable at the time to assume that its buprenorphine product would be approved by 1995 (it was in fact approved in 2002). However, as stated throughout this response, our reconsideration of the request for orphan-drug designation must be made based on the facts and circumstances at the time of the request.

buprenorphine.[104] As stated above, even if FDA were to assume that Indivior would obtain approval in 1995,[105] and analyze the sales of buprenorphine from that time to 2002, this would have resulted in at least two years of sales under a less rigidly-controlled market. In sum, FDA's assumptions about the size of the market for the first seven years of buprenorphine's marketing were not reasonable even if we were to take into account the actual length of time before the applicable regulatory framework was updated.

Finally, Indivior argues that the assumption that the relevant laws restricting access to treatment of OUD with opioids were unlikely to change was not relevant to FDA's orphan-drug designation determination.[106] As evidence, Indivior points to FDA's sensitivity analysis in the review of the amended request for orphan-drug designation to suggest that FDA accounted for potential increases in the eligible treatment population due to changes in the relevant laws and therefore did not rely on Indivior's assumption that the law was unlikely to be changed.[107] In fact, as explained below, the assumption that the relevant laws were unlikely to change was crucial to FDA's orphan-drug designation determination and FDA did not account for the impact of such a change in the sensitivity analyses.

FDA's review of Indivior's amended request for orphan-drug designation included a sensitivity analysis that analyzed nine scenarios, described in the background section above. Each scenario examined the effect of changing one or more of three figures presented by Indivior: (1) The years until marketing, (2) The share of the market that switches from methadone to buprenorphine, and (3) The estimated sales price. In these scenarios, the share of the market that switched to buprenorphine can be understood as the percent of methadone patients that switch to buprenorphine. In all of these scenarios, the number of total patients was constant at 104,000, the number provided by Indivior of the available patient population eligible for treatment with any opioid as controlled by the relevant laws at the time. However, FDA did acknowledge that in the scenarios where FDA increased the market share, that could act as a "surrogate" for increasing the total market.[108]

FDA's analysis showed buprenorphine becoming profitable in four of the scenarios where FDA did not rely on Indivior's assumptions and increased buprenorphine's market share. For example, chart 3A took the assumptions provided by Indivior, but assumed that 50% more patients switched from methadone to buprenorphine, which indicated a profit for Indivior. Because market share can be a surrogate for total market size if market share is assumed to be constant, an increase of the total market of 50% (104,000 to 156,000) would also have resulted in a profit. This demonstrates that slight changes to Indivior's assumptions would have resulted in buprenorphine becoming profitable. Nevertheless, FDA granted orphan-drug designation for buprenorphine. Those assumptions, including the assumption that it was unlikely the relevant laws controlling access to opioids for treating OUD would change over the first seven years of

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[104] O'Keeffe article, *supra* note 64 at S10.
[105] *See supra* note 100.
[106] Indivior July Comment, *supra* note 25, at 21-23.
[107] *Id.* at 21-22.
[108] For example, doubling the market share of 5% of 104,000 to 10% of 104,000 would have the same effect as doubling the total market to 208,000 while holding the market share to 5%.

marketing, and the assumption that the number of treatment facilities would not increase, thus appear to have formed the basis for FDA's decision to grant Indivior's orphan-drug designation request for buprenorphine.

Indivior is incorrect when it states that FDA "expressly considered potential regulatory changes that might substantially increase the accessible patient population" and that FDA "expressly considered the possibility of future increases in the available number of treatment slots."[109] Nothing in the FDA review explicitly analyzes what would happen if the relevant laws were liberalized, and the effect that would have on the total patient population. Additionally, nothing in the FDA review analyzes any other reason why the number of treatment facilities or treatment slots would not increase. At most, FDA analyzed the effect of increasing the total market by 50% or 100% (while holding market share constant), and as explained above, most of those scenarios showed a profit for Indivior.

At the time of the designation request, FDA estimated the total prevalence of OUD to be 1 to 1.5 million. It would have been reasonable to assume, at the time of designation, that changes to the relevant laws controlling access to treatment with opioids could have increased the total market by significantly more than the amounts implicitly accounted for by the Agency's sensitivity analysis. FDA's review did not consider the potential effects of regulatory changes and how those changes might impact both total market and the market penetration for buprenorphine. FDA thus did not analyze if it would be reasonable to assume that there would be no changes to the relevant laws to expand access to buprenorphine in light of the number of opioid users known to exist at the time.

In sum, given the nature of buprenorphine and the well-understood need for more widely available treatments for OUD, it was not reasonable to assume that the relevant laws restricting access to treatment of OUD with opioids were unlikely to change in a way that would increase the market for buprenorphine over the first seven year marketing period for the drug. FDA relied on that assumption, without explanation, to form the basis for the Agency's cost recovery determination. FDA also relied on the assumption that the number of treatment facilities would not increase during the first seven years of marketing. FDA's sensitivity analysis actually demonstrated the potential for Indivior to recover its costs for buprenorphine if there were slight changes to the market share of or total market size for buprenorphine. Because it was not reasonable to assume that the market size would remain constant for the first seven years of marketing of buprenorphine in the U.S., FDA's conclusion that there was no reasonable expectation that buprenorphine sales would recover Indivior's development costs was erroneous.

B. The cost recovery analysis was incomplete because it did not account for the cost and revenue associated with other potential buprenorphine products (including particular formulations and dosage forms)

In reviewing Indivior's request for designation, not only did FDA rely on unreasonable assumptions regarding total market size for the cost recovery analysis (as explained above), but FDA also improperly relied on information constrained to a particular formulation and dosage form of buprenorphine instead of considering information about the active moiety, including all

[109] Indivior July comment, *supra* note 25, at 22.

the products that could reasonably be expected to be developed with that active moiety. Therefore, FDA failed to consider information necessary to evaluate the designation request.

Because orphan-drug designation generally covers an active moiety for a specific rare disease or condition,[110] a cost recovery analysis should not be limited to just the particular product (such as a particular formulation and/or dosage form) described in the request for designation.[111] To comply with the statutory requirement that there is "no reasonable expectation" of cost recovery for the drug,[112] such analysis must also consider the costs and revenue that can reasonably be expected from all products with the active moiety (including alternative formulations and dosage forms) the sponsor can reasonably be expected to market during the first seven years of marketing the active moiety. Orphan-drug designation often occurs early in drug development, when sponsors can maximize the benefit from designation-associated incentives. At that point in development, a sponsor may not have determined the product it will ultimately market for the active moiety. Instead of requiring the sponsor to request orphan-drug designation for every possible product with the active moiety, the law, as FDA interprets it, only requires the sponsor to request designation for its active moiety for the rare disease or condition. Once an active moiety is designated, however, each product with the active moiety that the sponsor develops for the rare disease or condition will be covered by the orphan-drug designation. Because a sponsor may market multiple products with the same active moiety for the same disease or condition during the first seven years that the sponsor markets the active moiety for the disease or condition, FDA must account for all potential products with that active moiety (including alternative formulations and dosage forms) that may be reasonably developed when conducting a cost recovery analysis.

The potential for there to be multiple products with a particular active moiety can be relevant to each of the elements that are factored into a cost recovery analysis. For example, developing a new formulation or dosage form can factor in to the cost of development and the cost of production of the drug.[113] Additionally, the potential for there being different products with the active moiety could affect the different factors that determine the estimate of sales, including the market share of the drug and the price per dose of the drug.[114] For example, each particular product can have a different effect on how a drug is administered to the patient, the possible side effects, and its efficacy, which all can impact the price patients may be willing to pay for the drug and the expected market share the drug can penetrate.

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[110] *See* 21 CFR 316.3(b)(13)(i) (1993) (a drug is the same as another if it contains the same active moiety), 316.20(a)(a sponsor who wishes to obtain designation for a drug that is otherwise the same as a previously approved drug must provide a plausible hypothesis of clinical superiority).

[111] Finished drug products containing the same orphan-drug designated active moiety can vary in many ways, including in formulation or dosage form. Therefore a "product," as discussed in this section, is a particular formulation and/or dosage form of an active moiety.

[112] Section 526(a)(2)(B).

[113] 21 CFR § 316.21(c)(1) requires data on costs the sponsor has incurred that includes "dosage form development," which can be read to include development of any and all dosage forms that the sponsor is planning to develop, which could reasonably be marketed within the first seven years the sponsor is marketing the active moiety for the disease or condition.

[114] 21 CFR § 316.21(c)(6) requires the sponsor to estimate "revenues from sales of the drug in the United States during its first 7 years of marketing," which would include sales of any dosage form of the active moiety during the first seven years of marketing.

If sponsors were not required to account for all potential products with the active moiety, a sponsor could seek orphan-drug designation by providing information about a formulation or dosage form that is unlikely to recover costs, but then ultimately develop a different formulation or dosage form that will. For example, a sponsor could request designation based on a complex formulation of its active moiety that would be expensive to produce, be undesirable to patients, or penetrate a small portion of the market. Then, with the benefits of orphan-drug designation, the sponsor could develop a simpler, cheaper to produce, and more desirable formulation of the same active moiety for the same disease or condition.

Indivior's request for orphan-drug designation, and FDA's review of the request, only considered information regarding a single dosage form of buprenorphine (the sublingual tablet) for OUD, yet consistent with FDA's regulations and practice, Indivior obtained orphan-drug designation for the active moiety buprenorphine for the "treatment of opiate addiction in opiate users," not limited to a sublingual tablet dosage form.[115] To demonstrate that there was no reasonable expectation that the sponsor could recover the costs of development by selling the drug, FDA should have required, and the sponsor should have provided, information regarding other possible buprenorphine products (including alternative formulations and dosage forms) that Indivior could reasonably have been expected to develop. In the amended request for designation, Indivior stated there was a "need" for the sublingual presentation of buprenorphine for the treatment of OUD indication.[116] However, Indivior did not explain why the sublingual presentation was the only possible product for buprenorphine for the indication. Without analyzing the possibility of marketing other products, FDA did not obtain or consider all the information necessary for the Agency to properly conduct the cost recovery analysis.

Based on what was known at the time Indivior requested designation, it would have been reasonable to expect that other products with buprenorphine could be developed for the treatment of OUD. For example, a study published in 1978 in which buprenorphine was administered subcutaneously concluded that "addicts maintained on buprenorphine could be easily detoxified and possibly could be maintained on doses less frequently than once daily."[117] In addition, FDA approved an NDA for a parenteral dosage form of buprenorphine on December 29, 1981, for the treatment of pain.[118] Although this approval was for a different indication than OUD, paired with the fact that a parenteral dosage form of buprenorphine had been shown to have potential in treating OUD, it was reasonable at the time of designation to consider whether Indivior could develop a buprenorphine product other than the sublingual tablet. In the designation request, Indivior did not explain, and FDA did not analyze, whether it would also be appropriate for buprenorphine to be delivered in a different product for treatment of OUD.[119]

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[115] Buprenorphine designation letter, *supra* note 57 ("Please note that it is buprenorphine and not its formulation that has received orphan designation.").

[116] Amendment request, *supra* note 38 at 2.

[117] Jasinski, et al., *supra* note 73 at 515.

[118] Designation review, *supra* note 28 at 2 ("Buprenorphine is presently marketed in the United States as an injectable analgesic under NDA 18-401."). *See also* NDA 018401, Drugs@FDA, available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018401.

[119] *See generally* Amendment review, *supra* note 49. For the cost recovery analysis, the FDA review uses only the information provided by Indivior about the sublingual tablet form and does not discuss whether or not the cost

Consideration of developing and marketing another product with buprenorphine for OUD would have affected the cost and revenue calculations. For example, Indivior stated, "the need for a special unit dose sublingual presentation for this indication adds substantially to final product production costs compared to [methadone and LAAM] which can be supplied to treatment programs in bulk form."[120] It was clear that the dosage form of buprenorphine that Indivior chose to highlight at the time it requested designation was a factor in estimating the costs of production. Indivior did not justify the assumption that it would in fact only develop a sublingual dosage form of buprenorphine for treatment of OUD. Related to revenue, as stated above, the 1978 study concluded that patients with OUD could "possibly could be maintained on doses [of buprenorphine] less frequently than once daily."[121] Such a product, dosed less frequently than once daily, would be appealing to patients, which could have increased the market share of patients, or could have increased the price per dose that Indivior could expect to charge. Therefore, by failing to provide information about what other buprenorphine products could reasonably be developed, Indivior did not submit the information necessary to support a cost-recovery based orphan-drug designation, and the Agency erred in concluding that there was no reasonable expectation that Indivior could recover its development costs by marketing buprenorphine in the U.S.

III. Conclusion

Based on the facts and circumstances as of the date of the request for orphan-drug designation, FDA's decision that there was no reasonable expectation that the cost of developing and making available in the U.S. buprenorphine for "treatment of opiate addiction in opiate users" could be recovered from sales in the U.S. of buprenorphine for "treatment of opiate addiction in opiate users" was erroneous. Accordingly, FDA will revoke Indivior's orphan-drug designation for buprenorphine for "treatment of opiate addiction in opiate users" under 21 CFR § 316.29(a)(3).

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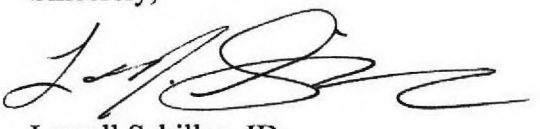
recovery analysis should also factor in other potential dosage forms of buprenorphine, such as a subcutaneous injection.

[119] *Id.* at 4.

[120] Amendment request, *supra* note 38 at 2.

[121] Jasinski, *supra* note 73 at 514.

Sincerely,



Lowell Schiller, JD
Principal Associate Commissioner for Policy

Enclosure 1 of 1

(b) (4)

11 November 1993

PRIVATE AND CONFIDENTIAL

RA Featherstone Esq
Reckitt & Colman Products Division
Dansom Lane
Hull
HU8 7DS

Dear Sir,

We understand that Reckitt & Colman Pharmaceuticals Inc have submitted an Orphan Drug Application to the US Food and Drug Administration for buprenorphine products ("BHD") for the treatment of opiate addiction.

In connection with that application you have asked us to review the calculations for the financial projection for BHD covering the period from 1993 to 2002. The financial projection comprises a projected cumulative return, together with notes of the assumptions on which it is based and a copy is attached for identification purposes. The financial projection is the sole responsibility of Reckitt & Colman Pharmaceuticals Inc.

We comment below on the principal assumptions made in compiling the financial projection.

1 **Sales to customers**

Sales to customers have been based on an estimate of the number of patients who will be prescribed BHD in preference to current treatments and the selling price per dose has been assumed at (b) (4) throughout the period of the projection.

2 **Contribution before marketing**

Contribution before marketing has been calculated as a constant percentage of sales to customers throughout the period of the projection. This reflects an assumption that the cost of raw materials and labour incurred by Reckitt & Colman will be constant. Contract packing charges in the US have been assumed, on the basis of existing costs to the National Institute of Drug Abuse ("NIDA") and price quotations provided to Reckitt & Colman, to be at the rate of (b) (4) per dose, and again this cost per dose has been assumed throughout the period of the projection.

(b) (4)

(b) (4)

3 Fixed costs and marketing

Fixed costs are based on the costs incurred by Reckitt & Colman Pharmaceuticals Inc during the 12 months to June 1993 and have been increased by (b) (4) annum compound over the period of the projection and apportioned between sales of BHD products and other products on the basis of the proportion of projected sales of BHD products to total projected sales of the company. Fixed costs also include costs to be incurred under a Cooperative Research and Development Agreement ("CRADA") between Reckitt & Colman Pharmaceuticals Inc and the National Institutes of Health totalling (b) (4)

Marketing costs comprise fixed and variable elements estimated by management to be (b) (4) respectively in 1995. The fixed element increases by (b) (4) annum thereafter and the variable element reduces in stages to a minimal amount in 1998.

4 Development costs

Development costs of (b) (4) are as estimated and detailed in the CRADA. These costs exclude the development costs already incurred by Reckitt & Colman in developing Buprenorphine. An amount of (b) (4) of the total development costs represents the use of a quantity of the active compound buprenorphine hydrochloride and this has been included at its normal sales price by Reckitt & Colman.

Development costs are written off as incurred in accordance with Reckitt & Colman accounting policy.

We emphasise that the projection covers an extended future period for a new product for which there are inherent risks and for this reason the actual results may vary considerably from those shown. The projection cannot be regarded as a forecast of profit or loss and we do not express or imply any opinion as to whether it will be achieved.

In our opinion, the projection, read in the context of the above, so far as the calculations are concerned has been properly compiled on the basis of the assumptions made by the company and is presented on a basis consistent with the generally accepted accounting principles and policies adopted by Reckitt & Colman.

You should appreciate that this report has been prepared on your instructions and is addressed to you and whilst we understand that a copy of it will be included in the company's submission to the Food and Drug Administration we do not accept any responsibility to either that party or any other party who may see our report.

Yours faithfully

Enclosure